Remarks

Reconsideration of this Application is respectfully requested. Claims 1, 4-12, 14, 20-41, 44-47, 50-54, 57 and 63-70 are pending in the application, with claims 1 and 63 being the independent claims. The specification has been amended only to comport the description of the figures to the drawings filed concurrently herewith. Applicants respectfully assert that no new matter has been added by way of the above amendments. Entry thereof and early notification is respectfully requested. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Summary of the Office Action

Claims 63-70 are allowed, and claims 1, 4-12, 14, 20-41, 44-47, 50-54 and 57 have been finally rejected under 35 U.S.C. § 103. There are no other outstanding objections or rejections.

Rejections under 35 U.S.C. § 103

Claims 1, 4-12, 14, 20-41, 44-47, 50-54 and 57 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Foster *et al.* (published PCT Application No. WO 96/33273, October 24, 1996) in view of Sharon *et al.* (Sharon, N. and Lis, H, "Legume lectins-- a large family of homologous proteins," *The FASEB J. 4*: 3198-3208 (1990)). Office Action, page 3, lines 4-6. Applicants traverse this rejection.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. In particular, the M.P.E.P. sets forth the criteria necessary to satisfy this burden:

> To establish a *prima facie* case of obviousness, three basic criteria *must* be met. First, there *must* be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there *must* be a reasonable expectation of success. Finally, the prior art reference (or references when combined) *must* teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success *must* both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

See M.P.E.P., Eighth ed., February revision, § 2142 "Legal Concept of *Prima Facie* Obviousness," (2003, emphasis added). For the reasons explained in the Amendment and Reply Under 37 C.F.R. § 1.111 (filed April 25, 2003), and which are wholly incorporated herein, Applicants respectfully assert that the references cited in support of the 35 U.S.C. § 103 rejection do not meet these criteria, and that consequently the Examiner has not established a *prima facie* case of obviousness.

The Examiner acknowledges that "Foster *et al.* do not disclose using a specific lectin such as galactose-binding lectin in preparing the . . . [claimed compositions]." Office Action, page 3, lines 20-21. The Examiner alleges, however, that this deficiency of Foster *et al.* can be cured by Sharon *et al.* which discloses certain galactose/N-acetylgalactosamine specific lectins. The alleged motivation for combining these two references is that "the galactose-binding lectins are widely available in legume plants (see Table 1 of Sharon *et al.*), can bind multivalent oligosaccharides having terminal galactose residues more specifically, and serve as a cell-recognition molecule for the

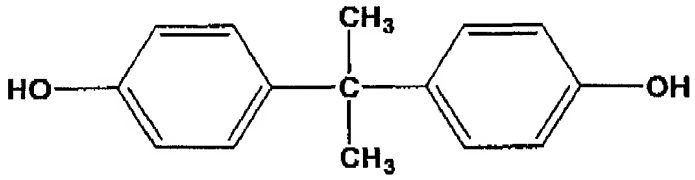
agent." *Id.* at page 4, lines 6-9. Applicants respectfully assert that this is an improper combination of references based solely on hindsight reasoning.

Foster *et al.* describe agents exhibiting specificity for peripheral sensory afferents. Foster *et al.*, Abstract. Although this references alludes to such agents comprising "lectins" at page 13, line 12, all of the working examples from page 16, line 18 to page 22, line 16 are limited to such agents comprising nerve growth factor and not comprising any lectin. Moreover, none of the specific prophetic examples listed from page 24, line 1 to page 25, line 15 include lectin, much less galactose-binding lectin. Hence, Foster *et al.* directs the skilled artisan away from such agents comprising lectin.

Sharon *et al.* would not suggest to the skilled artisan to modify the nerve growth factor compositions disclosed by Foster *et al.* with galactose-binding lectins. Sharon *et al.* is merely an academic review of the characterization and distribution of lectins. This reference presents information regarding galactose-binding lectins in the abstract, without any suggestion or motivation to the skilled artisan regarding their utility. Indeed, there is no indication in Sharon *et al.* that the galactose-binding lectins discussed therein are useful as analgesics. Hence, when attempting to address the technical problem of how to provide an improved analgesic effect, a skilled person would not consider Sharon *et al.* to be relevant, and would not make the combination with Foster *et al.* as alleged by the Examiner. Thus, the Examiner's allegation that Foster *et al.* can properly be modified by Sharon *et al.* represents improper hindsight reasoning.

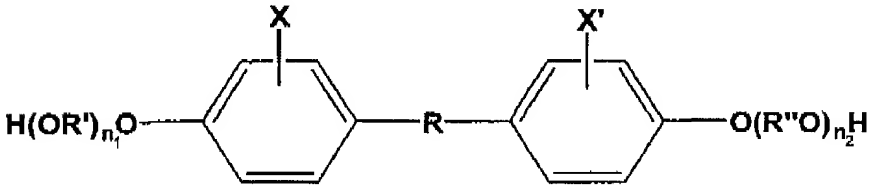
At best, the Examiner's contention that Applicants' claims are obvious in light of Foster *et al.* in view of Sharon *et al.* is analogous to the circumstances considered by the

Federal Circuit in *In re Baird*, 29 U.S.P.Q. 2d 1550 (Fed. Cir. 1994). In *In re Baird*, the Examiner rejected Baird *et al.*'s claims directed to a flash fusible toner comprising a polyester of bisphenol A and an aliphatic dicarboxylic acid as obvious over U.S. Patent 4,634,649 to Knapp *et al.* *Id.* at 1551. Bisphenol A is described in Baird *et al.*'s application as having the following structure:



Knapp *et al.* teach developer compositions comprising

> the polymeric esterification product of a dicarboxylic acid and a diphenol of the following generic formula:



> wherein R is selected from substituted and unsubstituted alkylene radicals having from about 2 to about 12 carbon atoms, alkylidene radicals having from 1 to 12 carbon atoms and cycloalkylidene radicals having from 3 to 12 carbons atoms; R' and R" are selected from substituted and unsubstituted alkylene radicals having from 2 to 12 carbon atoms, alkylene arylene radicals having from 8 to 12 carbon atoms and arylene radicals; X and X' are selected from hydrogen or an alkyl radical having from 1 to 4 carbon atoms; and each n is a number from 0 (zero) to 4.

Id. at 1551. The Examiner's obviousness rejection was made on the grounds that Knapp *et al.* describe a generic formula which encompasses bisphenol A[1].

[1] Note that the dicarboxylic acids claimed by Baird *et al.* were specifically described by Knapp *et al.*

The judicial opinion describes the motivation presented by the Examiner for the obviousness rejection as follows:

> Recognizing that bisphenol A is defined when certain specific variables are chosen, the examiner reasoned that bisphenol A "may be easily derived from the generic formula of the diphenol in [Knapp] and all the motivation the worker of ordinary skill in the art needs to arrive at the particular polyester of the instant claim[] is to follow [that formula]."

Id. (omissions in original). In upholding the Examiner's rejection, the Board of Patent Appeals and Interferences ("Board") stated that "the fact that [the claimed] binder resin is clearly encompassed by the generic disclosure of Knapp . . . provides ample motivation for the selection of [the claimed composition]." *Id.*

On appeal to the Federal Circuit, the court reversed both the Board and the Examiner. In particular, the court stated that

> [t]he fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350, 21 U.S.P.Q.2D (BNA) 1941, 1943 (Fed. Cir. 1992) (rejecting Commissioner's argument that "regardless [] how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it"). *Jones* involved an obviousness rejection of a claim to a specific compound, the 2-(2'-aminoethoxy)ethanol salt of 2-methoxy-3,6-dichlorobenzoic acid (dicamba), as obvious in view of, *inter alia*, a prior art reference disclosing a genus which admittedly encompassed the claimed salt. We reversed the Board's rejection, reasoning that the prior art reference encompassed a "potentially infinite genus" of salts of dicamba and listed several such salts, but that it did not disclose or suggest the claimed salt. *Id.*
>
> In the instant case, the generic diphenol formula disclosed in Knapp contains a large number of variables, and we estimate that it encompasses more than 100 million different diphenols, only one of which is bisphenol A. While the Knapp formula unquestionably encompasses bisphenol A when specific variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables. Indeed, Knapp appears to teach away from the selection of bisphenol A . . . .

Id. at 1552 (second omission in original). Hence, prior art references that disclose a broad class of compositions which encompasses a specifically claimed composition or subset of compositions do not necessarily render that claimed composition or subset of compositions obvious. Motivation for the skilled artisan to make a claimed composition or subset of compositions does not derive merely from the fact that the prior art describes a class of compositions broad enough to encompass that which is claimed.

Here, Foster *et al.* describe a broad class of compositions which include "one embodiment . . . [in which] the LH_N fragment of a clostridial neurotoxin is covalently linked, using linkages which may include one or more spacer regions, to a TM." Foster *et al.*, page 13, lines 21-24. However, TM is defined by Foster *et al.* very broadly:

> Targeting Moiety (TM) means *any* chemical structure of an agent which functionally interacts with a binding site causing a physical association between the agent and the surface of a primary sensory afferent.

Foster *et al.*, page 9, lines 16-18 (emphasis added). Exemplary TMs are also only listed in a very general manner:

> The TM component of the agent can comprise one of many cell binding molecules, including, but not limited to, antibodies, monoclonal antibodies, antibody fragments (Fab, $F(ab)'_2$, Fv, ScFv, etc.), lectins and ligands to the receptors for hormones, cytokines, growth factors or neuropeptides. A list of possible TMs is given in Table 1, this list is illustrative and is not intended to be limiting to the scope of TMs which could fulfil the requirements of this invention.

Foster *et al.*, page 13, lines 9-15. The term "lectins" is not further specified. Moreover, the working examples of Foster *et al.* only describe nerve growth factor as the TM, and thus teach away from lectins or galactose-binding lectins. *Id.* at page 16, line 18 to page 22, line 16. The prophetic examples of *possible* TMs listed in Table 1 on

pages 24-25 of Foster *et al.* do not even include lectins, much less galactose binding lectins.

Lectins are an extremely diverse group of molecules having a plethora of different binding abilities. For example, as described in Sharon *et al.*, at least 70 lectins have been isolated from leguminous plants alone, and many more are widely distributed in animals, insects, non-legume plants and microorganisms. Sharon *et al.*, first line of Abstract, and first paragraph on page 3198. These lectins vary markedly with regard to their specificity, and may bind to numerous different sugar groups (including combinations thereof) such as mannose, glucose, galactose, N-acetylgalactosamine, N-acetylglucosamine, and L-fucose. *Id.* at page 3198, left column, lines 1-4, and page 3199, Table 1. The above-mentioned diverse binding ability of lectins is best illustrated by reference to Yamazaki, N. *et al.*, "Endogenous lectins as targets for drug delivery," *Advanced Drug Delivery Reviews 43*: 225-244 (2000), previously submitted as reference AS9 in an IDS filed September 10, 2002. Yamazaki *et al.* discuss the concept of the "sugar code." In more detail, Yamazaki *et al.* teach that, due to the diverse range of sugar monomers, modifications and multimeric organizations thereof, a vast number of glycol-structures may exist in nature, with the result that the binding ability of lectins may be equally vast. *See* Yamazaki *et al.*, Abstract, and part 2 beginning on page 226, especially page 227, left column, lines 11-14. Indeed, an NCBI search for lectin proteins reveals over 4600 specific lectins. Exhibit A, provided herewith (printout only of the first of 231 screens).

While lectins as a genus demonstrate a diverse range of binding abilities, the present invention is concerned only with the use of a specific sub-group thereof, namely

galatcose-binding lectins, for the explicit purpose of targeting clostridial neurotoxins to pain-sensing cells.

Applicants respectfully assert that the Examiner has not set forth a *prima facie* case of obviousness. However, even assuming that the Examiner has established a *prima facie* case of obviousness, Applicants submit that the unexpected results described in the specification overcome any basis for rejection that the Examiner may assert. The M.P.E.P. provides that such results, as provided by Applicants' specification, must be considered:

> If the examiner determines there is factual support for rejecting the claimed invention under 35 U.S.C. 103, the examiner must then consider any evidence supporting the patentability of the claimed invention, such as any evidence in the specification or any other evidence submitted by the applicant. The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it. With regard to rejections under 35 U.S.C. 103, the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a *prima facie* case of obviousness) is more probable than not.

M.P.E.P., Eighth ed., § 2142, Legal Concept of *Prima Facie* Obviousness (February 2003 revision). Applicants respectfully assert that upon consideration of the data set forth in Applicants' specification (and which is repeated herein), the preponderance of evidence demonstrates that a *prima facie* case of obviousness has not been established.

An important data comparison relevant to assessing the effectiveness of an analgesic molecule is a comparison of the IC_{50} values for dorsal root ganglia (eDRG) cells (i.e., pain-sensing cells) over spinal cord (eSC) cells. In this respect, a low IC_{50} value alone does not necessarily indicate a preferred analgesic agent. For example, if a

conjugate demonstrates a low IC_{50} value for both eDRG and eSC, then such a conjugate lacks a desired selectivity for pain-sensing cells. Thus, a preferred property of an analgesic molecule is that it demonstrates a low IC_{50} ratio value as determined by:

$$\frac{IC_{50} \text{ for eDRG}}{IC_{50} \text{ for eSC}}$$

Measuring a composition's effectiveness using this ratio is described in Applicants' specification, for example, at page 17, lines 3-21.

Referring to Examples 4, 5 and 7 and Figures 6 to 8 of Applicants' specification, it is clear that the claimed agents comprising a galactose-binding lectin demonstrate a significantly superior ratio value (based on the above formula) than do other structurally related conjugates containing a lectin that is not a galactose-binding lectin. Conjugates comprising non-galactose-binding lectins are not encompassed by Applicant's claims.

The galactose-binding ExL-containing conjugate of Example 4 demonstrates an IC_{50} for eDRG of 3.66. Specification, page 20, lines 20-21. Referring to Figure 6, the extrapolated corresponding IC_{50} for eSC for this ExL-containing conjugate is in excess of 2000. Thus, the IC_{50} ratio for this galactose-binding lectin containing conjugate is less than 0.001. Similarly, the galactose-binding lectin soya bean agglutinin (SBA) conjugate of Example 5 demonstrates an IC_{50} for eDRG of 4.72 (i.e., an average of the 2 values at line 29 on page 21 of Applicants' specification). An extrapolation of Figure 7 provides a corresponding IC_{50} for eSC for this SBA conjugate in excess of 100. Thus, the ratio for this galactose-binding lectin conjugate is less than 0.04. In contrast, the IC_{50} values for eDRG and eSC for the non-galactose-binding wheat germ agglutinin-based lectin conjugate of Example 7 are 0.34 and 0.06 respectively, giving the relatively high IC_{50} ratio value of 5.6. Specification, page 22, lines 19-22. Thus, the ExL- and SBA-

galactose-binding lectin based conjugates respectively demonstrate greater than 5000- or 100-fold superior IC_{50} ratios relative to that for the non-galactose binding WGA-based lectin conjugate.

Figures 6 and 7 further demonstrate the claimed conjugates' improved selectivity for DRG (pain-sensing) cells over SC cells. For example, at a concentration of 10 μg protein conjugate/ml, the conjugates of the present invention surprisingly demonstrate at most 2-15% background inhibition of the neurotransmitter glycine from SC cells. Specification, figures 6 and 7. In contrast, Figure 8 demonstrates that a conjugate having a targeting moiety that is a non-galactose-binding lectin exhibits a much higher (approximately 70%) background inhibition of glycine from SC cells at this same protein conjugate concentration.

Hence, the galactose-binding lectin conjugates of the present invention demonstrate superior specificity for pain-sensing cells and hence superior analgesic properties as compared to non-galactose-binding lectin-containing clostridial conjugates. Neither Foster *et al.* alone, or Foster *et al.* in combination with Sharon *et al.* teach or suggest the unexpectedly improved targeting specificity for pain-sensing cells (or the associated enhanced analgesic effect) that is achieved by the use of galactose-binding lectins in accordance with Applicants' invention. Applicants respectfully assert that such unexpected results overcome any basis for *prima facie* obviousness under 35 U.S.C. § 103.

Applicants respectfully submit that the preponderance of the evidence does not show that a *prima facie* case of obviousness has been made. Accordingly, Applicants

respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 4-12, 14, 20-41, 44-47, 50-54 and 57 under 35 U.S.C. § 103(a).

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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